(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 July 2004 (08.07.2004)

PCT

(10) International Publication Number
WO 2004/056748 A1

(51) International Patent Classification[7]: C07C 235/20, A61K 31/16

(21) International Application Number:
PCT/GB2003/005602

(22) International Filing Date:
19 December 2003 (19.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0229931.1 21 December 2002 (21.12.2002) GB

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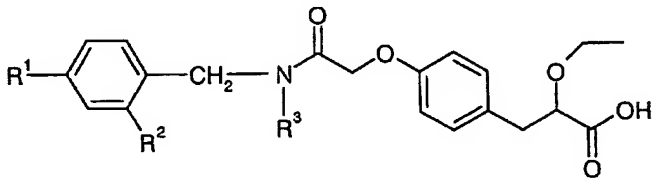
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: THERAPEUTIC AGENTS



(I)

(57) Abstract: The present invention provides the S enantiomer of a compound of formula (I) wherein R^1 represents chloro, trifluoromethyl or trifluoromethoxy, R^2 represents H or fluoro and R^3 represents a C_{2-4}alkyl group as well as pharmaceutically acceptable salts, solvates and prodrugs thereof, to processes for preparing such compounds, to their the utility in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance, to methods for their therapeutic use and to pharmaceutical compositions containing them.

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THERAPEUTIC AGENTS

Field of the invention

The present invention relates to certain novel (2*S*)-3-(4-{2-[amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid derivatives, to processes for preparing such compounds, to their utility in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome, to methods for their therapeutic use and to pharmaceutical compositions containing them.

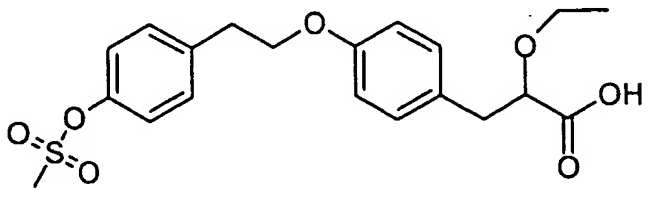
Background of the invention

The metabolic syndrome including type 2 diabetes mellitus, refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinaemia, possibly type 2 diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidaemia observed as deranged lipoprotein levels typically characterised by elevated VLDL (very low density lipoproteins), small dense LDL particles and reduced HDL (high density lipoprotein) concentrations and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In type 2 diabetes mellitus atherosclerosis related conditions cause up to 80% of all deaths.

In clinical medicine there is awareness of the need to increase the insulin sensitivity in patients with the metabolic syndrome and thus to correct the dyslipidaemia which is considered to cause the accelerated progress of atherosclerosis. However, currently this is not a universally accepted diagnosis with well-defined pharmacotherapeutic indications.

The S-enantiomer of the compound of formula C below



C

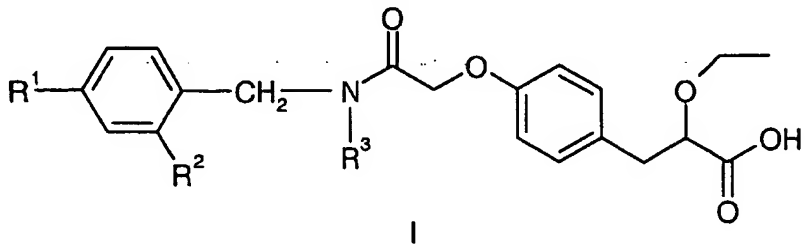
2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid, is disclosed in PCT Publication Number WO99/62872. This compound is reported to be a modulator of peroxisome proliferator-activated receptors (PPAR, for a review of the PPARs see T. M.Willson et al , J Med Chem 2000, Vol 43, 527) and has combined PPARα/PPARγ agonist

activity (Structure, 2001, Vol 9, 699, P. Cronet et al). This compound is effective in treating conditions associated with insulin resistance.

Surprisingly a series of compounds has now been found which are selective PPARα modulators.

Description of the invention

The present invention provides the S enantiomer of a compound of formula I



I

wherein R^1 represents chloro, trifluoromethyl or trifluoromethoxy, R^2 represents H or fluoro and R^3 represents a C_{2-4}alkyl group as well as pharmaceutically acceptable salts, solvates and prodrugs thereof.

The term "prodrug" as used in this specification includes derivatives of the carboxylic acid group which are converted in a mammal, particularly a human, into the carboxylic acid group or a salt or conjugate thereof. It should be understood that, whilst not being bound by theory, it is believed that most of the activity associated with the prodrugs arises from the activity of the compound of formula I into which the prodrugs are converted. Prodrugs can be prepared by routine methodology well within the capabilities of someone skilled in the art. Various prodrugs of carboxy are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology. **42**: 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p.113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, **8**:1-38 (1992);

d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, **77**:285 (1988); and

e) N. Kakeya, *et al.*, Chem Pharm Bull, **32**:692 (1984).

The above documents a to e are herein incorporated by reference.

In vivo cleavable esters are just one type of prodrug of the parent molecule. An *in vivo* hydrolysable (or cleavable) ester of a compound of the formula (I) that contains a carboxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human

or animal body to produce the parent acid. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters, for example, methoxymethyl; C_{1-6}alkanoyloxymethyl esters, for example, pivaloyloxymethyl; phthalidyl esters; C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters, for example, 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example, 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters, for example, 1-methoxycarbonyloxyethyl; and may be formed at any carboxy group in the compounds of this invention.

Specific compounds of the invention are:

(2*S*)-3-[4-(2-{Butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxy propanoic acid;

(2*S*)-3-(4-{2-[(4-Chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid;

(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]-propanoic acid;

(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl] propanoic acid; and

(2*S*)-3-[4-(2-{Butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid;

and pharmaceutically acceptable salts and solvates thereof.

It should be understood that each of the above compounds individually and also any combination of these compounds for example two, three, four or all of the above compounds forms part of the present invention.

It should also be understood that the present invention includes the five embodiments in which each of the above five compounds is in turn excluded from the generic claim to a compound of formula I, as described above, by means of a proviso to that compound. The present invention also includes embodiments wherein any combination of the five compounds above is excluded from the generic claim to a compound of formula I, as described above, by means of a proviso to that combination of compounds.

In the present specification the expression "pharmaceutically acceptable salts" is intended to define but is not limited to base salts such as the alkali metal salts, alkaline earth metal salts, ammonium salts, salts with basic amino acids, and salts with organic amines, particularly *tert*-butylamine.

In another aspect the present invention provides one or more of the following:

(2*S*)-3-[4-(2-{Butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxy propanoic acid *tert*-butylammonium salt;

(2*S*)-3-(4-{2-[(4-Chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid *tert*-butylammonium salt;

(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]-propanoic acid *tert*-butylammonium salt;

(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl] propanoic acid *tert*-butylammonium salt; and

(2*S*)-3-[4-(2-{Butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid *tert*-butylammonium salt.

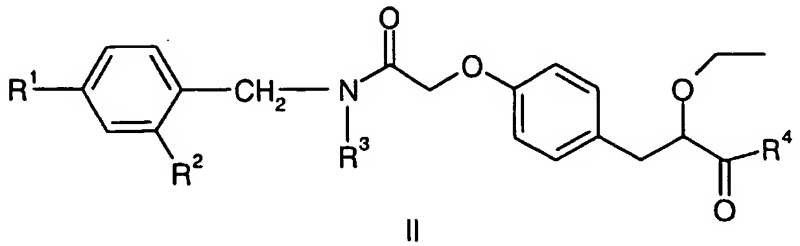
These salts may be prepared by reacting an acid with *tert*-butylamine (for example around a molar equivalent with respect to the acid) in a solvent for example an ether e.g. diisopropyl ether or *tert*-butylmethyl ether or an ester e.g. *tert*-butyl acetate or mixtures thereof or from a mixture of one of these solvents and an anti-solvent for example a hydrocarbon e.g. isooctane and isolating the salt by methods known to those skilled in the art for example by filtration.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms. Certain compounds of the present invention may exist as tautomers. It is to be understood that the present invention encompasses all such tautomers.

Methods of preparation

The compounds of the invention may be prepared as outlined below. However, the invention is not limited to these methods. The compounds may also be prepared as described for structurally related compounds in the prior art. The reactions can be carried out according to standard procedures or as described in the experimental section.

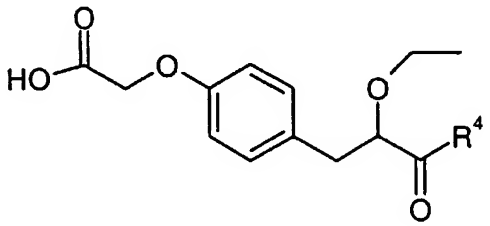
Compounds of formula I may be prepared by reacting the S-enantiomer of a compound of formula II



II

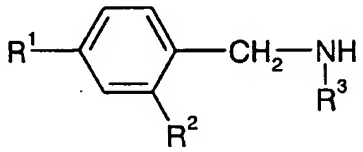
in which R^1, R^2 and R^3 are as previously defined and R^4 represents a protecting group for a carboxylic hydroxy group as described in the standard text "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts, with a de-protecting agent. The protecting group may also be a resin, such as Wang resin or 2-chlorotrityl chloride resin. Protecting groups may be removed in accordance to techniques which are well known to those skilled in the art. One such protecting group is where R^4 represents a C_{1-6}alkoxy group for example methoxy or ethoxy or an arylalkoxy group eg benzyloxy, such that COR^4 represents an ester. Such esters can be reacted with a de-protecting agent e.g. a hydrolysing agent, for example lithium hydroxide in a mixture of THF and water, at a temperature in the range of 0-100°C to give compounds of formula I.

Compounds of formula II may be prepared by reacting the S-enantiomer of a compound of formula III



III

in which R^4 is as previously defined with a compound of formula IV



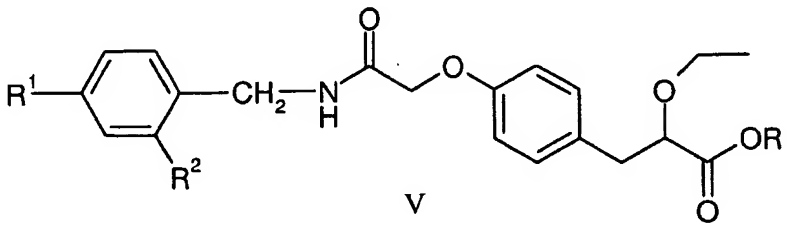
IV

in which R^1, R^2 and R^3 are as previously defined in an inert solvent, for example dichloromethane, in the presence of a coupling agent, for example a carbodimide, eg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide , and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylaminopyridine, at a temperature in the range of -25°C to 150°C.

Compounds of formula III and IV may be prepared by methods described in the Examples or by analogous methods known to those skilled in the art.

Compounds of formula II and III are useful intermediates in the preparation of compounds of formula I and are believed to be novel. Compounds of formula II and III are herein claimed as a further aspect of the present invention. The S-enantiomers of compounds of formula II and III are preferred.

Compounds of formula I may be also prepared by reacting a compound of formula V,



V

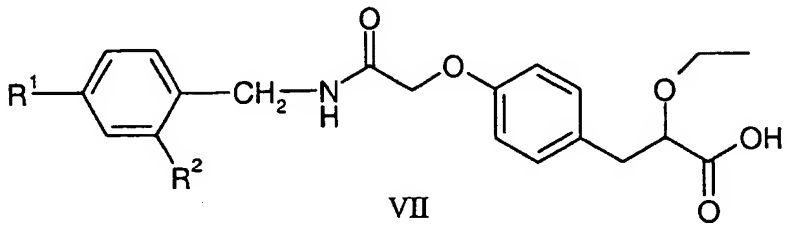
in which R^1 and R^2 are as previously defined, R is H or OR represents a protecting group for a carboxylic hydroxy group with a compound of formula VI

R^3X

VI

wherein R^3 is as previously defined and X is a leaving group, in the presence of a base in the presence of an inert solvent at a temperature in the range -25°C to 150°C and optionally, when OR represents a protecting group, removal of the protecting group.

In particular a compound of formula I may be prepared by reacting a compound of formula VII



VII

in which R^1 and R^2 are as previously defined with a compound of formula VI

R^3X

VI

wherein R^3 is as previously defined and X is a leaving group in the presence of a base in the presence of an inert solvent at a temperature in the range -25°C to 150°C.

The protecting groups OR and deprotecting agents are described in the standard text "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts, which is herein incorporated by reference. Suitable protecting groups include where OR represents a C_{1-6}alkoxy group eg methoxy or ethoxy group or an arylalkoxy group eg benzyloxy. In particular, when OR represents a C_{1-6}alkoxy group eg ethoxy group or an arylalkoxy group eg benzyloxy, such that COOR represents an ester then such esters may be reacted with a de-protecting agent e.g. a hydrolysing agent, for example lithium hydroxide in a mixture of THF and water, at a temperature in the range of 0-100°C.

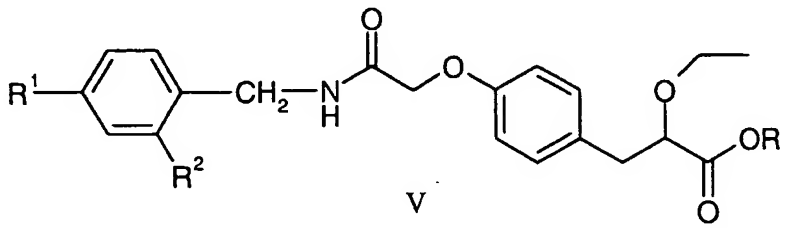
Suitable bases include potassium hydroxide, sodium hydroxide, lithium hydroxide, sodium hydride, potassium *tert*-butoxide, cesium carbonate, potassium carbonate, or sodium carbonate particularly potassium hydroxide.

Suitable inert solvents include dimethyl sulphoxide, *N,N*-dimethylformamide, *N*-methylpyrrolidone or toluene or mixtures thereof, particularly dimethyl sulphoxide.

Suitably X represents bromo, chloro, OSO_2CH_3, OTosyl, OSO_2CF_3, OC(O)OR, $OP(O)(OR)_2$ or OSO_2OR. Particularly X is chloro or bromo.

Optionally a phase transfer catalyst may be used for example an alkylammonium salt for example a tetraalkylammonium halide salt eg tetrabutyl ammonium bromide.

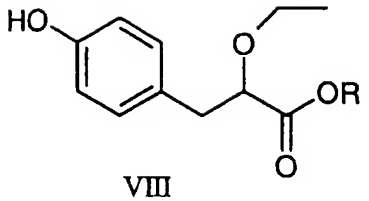
Compounds of formula V in which R is H (or compound VII) may be prepared by reacting a compound of formula V



V

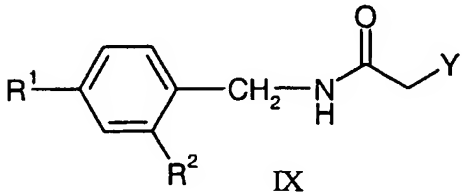
in which R^1 and R^2 are as previously defined and OR represents a protecting group for a carboxylic hydroxy group with a de-protecting agent. In particular, OR represents a C_{1-6}alkoxy group eg ethoxy group or an arylalkoxy group eg benzyloxy, such that COOR represents an ester. Such esters can be reacted with a de-protecting agent e.g. a hydrolysing agent, for example lithium hydroxide in a mixture of THF and water, at a temperature in the range of 0-100°C.

Compounds of formula V in which OR represents a protecting group for a carboxylic hydroxy group may be prepared by reacting a compound of formula VIII



VIII

in which OR is as previously defined with a compound of formula IX



IX

in which R^1 and R^2 are as previously defined and Y represents a leaving group, for example halo, particularly chloro, in an inert solvent, for example acetonitrile or methyl isobutylketone, in the presence of a base, for example potassium carbonate, at a temperature in the range of 0°C to 150°C.

It is believed that the compounds of formula V in which R is H (compound VII), for example (2*S*)-3-[4-(2-{[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxy propanoic acid;

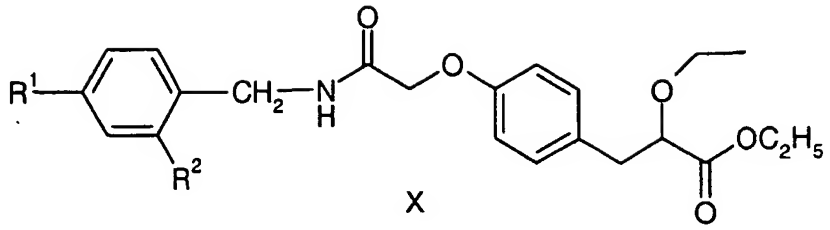
(2*S*)-3-(4-{2-[4-Chlorobenzylamino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid;

(2*S*)-2-Ethoxy-3-[4-(2-{4-(trifluoromethoxy)benzylamino}-2-oxoethoxy)phenyl]propanoic acid; and

(2*S*)-2-Ethoxy-3-[4-(2-{4-(trifluoromethyl)benzylamino}-2-oxoethoxy)phenyl] propanoic acid;

are novel and are herein claimed as a further part of the present invention. These compounds have the advantage of being solid and therefore offer an opportunity for purification and isolation during the reaction sequence if desired. These compounds are also modulators of PPAR alpha and /or PPAR gamma and are believed to be useful in treating the indications described herein.

Also claimed herein is a compound of formula V in which OR represents a protecting group for a carboxylic hydroxy group in particular OR represents for example a C_{1-6}alkoxy group eg methoxy, ethoxy or propoxy or an arylalkoxy group wherein aryl is phenyl optionally substituted by C_{1-6}alkyl, C_{1-6}alkoxy or halo, eg benzyloxy, for example a compound of formula X



X

in which R^1 and R^2 are as previously defined.

In another aspect the present invention provides a process for preparing a pharmaceutically acceptable salt of the compound of formula I comprising reacting the acid obtained by one of the processes of the present invention with a base, optionally in the presence of a solvent and isolating the salt.

Preferably the compound of formula I prepared by the process is the (2S)-enantiomer.

Similarly the preferred compounds of formulae V and X are the (2S)-enantiomer

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

The expression "inert solvent" refers to a solvent that does not react with the starting materials, reagents, intermediates or products in a manner that adversely affects the yield of the desired product.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free acid, or a pharmaceutical acceptable organic or inorganic base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in therapeutical treatment of humans are about 0.0001-100 mg/kg body weight, preferably 0.001-10 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The present compounds of formula (I) are useful for the prophylaxis and/or treatment of clinical conditions associated with inherent or induced reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders (also known as metabolic syndrome). These clinical conditions will include, but will not be limited to, general obesity, abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia, type 2 diabetes and the dyslipidaemia characteristically appearing with insulin resistance. This dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoprotein (VLDL) triglyceride rich particles, high Apo B levels, low high density lipoprotein (HDL) levels associated with low apoAI particle levels and high Apo B levels in the presence of small, dense, low density lipoproteins (LDL) particles, phenotype B.

The compounds of the present invention are expected to be useful in treating patients with combined or mixed hyperlipidemias or various degrees of hypertriglyceridemias and postprandial dyslipidemia with or without other manifestations of the metabolic syndrome.

Treatment with the present compounds is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as well as antiinflammatory properties. The cardiovascular disease conditions include macro-angiopathies of various internal organs causing myocardial infarction, congestive heart failure, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of their insulin sensitizing effect the compounds of formula I are also expected to prevent or delay the development of type 2 diabetes from the metabolic syndrome and diabetes of pregnancy. Therefore the development of long-term complications associated with chronic hyperglycaemia in diabetes mellitus such as the micro-angiopathies causing renal disease, retinal damage and peripheral vascular disease of the lower limbs are expected to be delayed. Furthermore the compounds may be useful in treatment of various conditions outside the cardiovascular system whether or not associated with insulin resistance, like polycystic ovarian syndrome, obesity, cancer and states of inflammatory disease including neurodegenerative disorders such as mild cognitive impairment, Alzheimer's disease, Parkinson's disease and multiple sclerosis. The compounds may be useful in treatment of psoriasis.

The compounds of the present invention are expected to be useful in controlling glucose levels in patients suffering from type 2 diabetes.

The present invention provides a method of treating or preventing dyslipidemias, the insulin resistance syndrome and/or metabolic disorders (as defined above) comprising the administration of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating or preventing type 2 diabetes comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating or preventing atherosclerosis comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

In a further aspect the present invention provides the use of a compound of formula I as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment of insulin resistance and/or metabolic disorders.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, for example metformin, phenformin and buformin, insulin (synthetic insulin analogues, amylin) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors). An example of an alpha-glucosidase inhibitor is acarbose or voglibose or miglitol. An example of a prandial glucose regulator is repaglinide or nateglinide.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with another PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to NN622/Ragaglitazar, BMS 298585, WY-14643, clofibrate, fenofibrate, bezafibrate, gemfibrozil and ciprofibrate; GW 9578, ciglitazone, troglitazone, pioglitazone, rosiglitazone, eglitazone, proglitazone, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-

methanesulphonyloxyphenyl}ethoxy)-phenyl]propanoic acid and pharmaceutically acceptable salts thereof.

In addition the combination of the invention may be used in conjunction with a sulfonylurea for example: glimepiride, glibenclamide (glyburide), gliclazide, glipizide, gliquidone, chloropropamide, tolbutamide, acetohexamide, glycopyramide, carbutamide, glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolcylamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. Therefore the present invention includes administration of a compound of the present invention in conjunction with one, two or more existing therapies described in this paragraph. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated complications will be those known in the art and approved for use by regulatory bodies for example the FDA and may be found in the Orange Book published by the FDA. Alternatively smaller doses may be used as a result of the benefits derived from the combination. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, bervastatin, cerivastatin, dalvastatin, fluvastatin, itavastatin, lovastatin, mevastatin, nicostatin, nivastatin, pravastatin and simvastatin, or a pharmaceutically acceptable salt, especially sodium or calcium, or a solvate thereof, or a solvate of such a salt. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A particularly preferred statin is, however, a compound with the chemical name (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, [also known as (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[*N*-methyl-*N*-(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt. The compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl-(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, and its calcium and sodium salts are disclosed in European Patent Application, Publication No. EP-A-0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444. This latter statin is now known under its generic name rosuvastatin.

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor).

Suitable compounds possessing IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818, WO 98/38182, WO 99/32478, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 00/62810, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/32428, WO 02/50051, EP 864 582, EP489423, EP549967, EP573848, EP624593, EP624594, EP624595 and EP624596 and the contents of these patent applications are incorporated herein by reference.

Particular classes of IBAT inhibitors suitable for use in the present invention are benzothiepines, and the compounds described in the claims, particularly claim 1, of WO 00/01687, WO 96/08484 and WO 97/33882 are incorporated herein by reference. Other suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

One particular suitable compound possessing IBAT inhibitory activity is (3*R*,5*R*)-3-butyl-3-ethyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl β-D-glucopyranosiduronic acid (EP 864 582). Other suitable IBAT inhibitors include one of:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl) carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(5-carboxypentyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{(R)-1-[*N''*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]-2-hydroxyethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-((ethoxy)(methyl)phosphoryl-methyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(hydroxy)(methyl)phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-methylthio-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(ethyl) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(hydroxy) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[(R)-*N'*-(2-methylsulphinyl-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-[*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-{(S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R/S)-α-{*N*-[1-(R)-2-(S)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl}-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;

a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;

a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;

a nicotinic acid derivative, including slow release and combination products, for example, nicotinic acid (niacin), acipimox and niceritrol;

a phytosterol compound for example stanols;

probucol;

an omega-3 fatty acid for example Omacor™;

an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker for example metoprolol, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a CB1 antagonist or inverse agonist for example as described in WO01/70700 and EP 65635 ;

aspirin;

a Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in combination with a compound of formula I include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril,

epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of formula I include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this

combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;

b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Examples

^{1}H NMR and ^{13}C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at ^{1}H frequencies of 300, 400, 500 and 600 MHz, respectively, and at ^{13}C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale (δ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Abbreviations

DMSO	dimethyl sulfoxide
THF	tetrahydrofuran
Pd/C	palladium on charcoal
DMAP	dimethylaminopyridine
t	triplet
s	singlet
d	doublet
q	quartet
m	multiplet
bs	broad singlet
dm	doublet of multiplet
bt	broad triplet
dd	doublet of doublet

Example 1

(2*S*)-3-[4-(2-{Butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxy propanoic acid

(i) Ethyl (2*S*)-3-{4-[2-(benzyloxy)-2-oxoethoxy]phenyl}-2-ethoxypropanoate

To a solution of ethyl (2*S*)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (23.8 g, 100 mmol, prepared as described in WO99/62872) in acetonitrile (200 mL) was added anhydrous potassium carbonate (31.9 g, 231 mmol) followed by benzyl bromoacetate (17.4 mL, 110 mmol) and the reaction mixture was refluxed overnight. The reaction mixture was allowed to cool to room temperature, insoluble salts were filtered off and the solution was concentrated *in vacuo*. The residue was taken up in ethyl acetate (300 mL), and the organic phase was washed with aqueous $NaHCO_3$ (3 x 100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification on silica gel with methylene chloride as the eluent and collection of pure fractions yielded 22.4 g (58%) of a yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, 3H), 1.22 (t, 3H), 2.93–2.97 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.64 (s, 2H), 5.23 (s, 2H), 6.82 (d, 2H), 7.15 (d, 2H), 7.32–7.39 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 15.2, 38.6, 60.9, 65.6, 66.3, 67.0, 80.4, 114.6, 128.5, 128.6, 128.7, 130.6, 135.3, 156.7, 169.0, 172.6.

(ii) {4-[(2*S*)-2,3-Diethoxy-3-oxopropyl]phenoxy}acetic acid

To a solution of ethyl (2*S*)-3-{4-[2-(benzyloxy)-2-oxoethoxy]phenyl}-2-ethoxypropanoate (22.33 g, 57.8 mmol) in freshly distilled THF (290 mL) was added Pd/C (10%, 3.1 g) and the reaction mixture was hydrogenated under atmospheric pressure at room temperature overnight. The mixture was filtered through a plug of Celite and the filtrate was concentrated *in vacuo* to afford 16.6 g (97%) of a light yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, 3H), 1.21 (t, 3H), 2.93–2.98 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.65 (s, 2H), 6.84 (d, 2H), 7.17 (d, 2H), 8.48 (bs, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 15.1, 38.5, 61.0, 65.1, 66.4, 80.3, 114.6, 130.7, 130.9, 156.4, 172.7, 173.7

(iii) *N*-Butyl-*N*-[2-fluoro-4-(trifluoromethyl)benzyl]amine

To a solution of 2-fluoro-4-(trifluoromethyl)benzaldehyde (3.84 g, 20.0 mmol) and *n*-butylamine (1.46 g, 20.0 mmol) in methanol (100 mL) were added acetic acid (4.6 mL, 80 mmol) and sodium cyanoborohydride (1.51 g, 24.0 mmol) and the solution was stirred at room temperature for 3 days. Water (10 mL) was added and the mixture was concentrated *in vacuo*. The residue was taken up in aqueous 1 M KOH (125 mL) and ethyl acetate (100 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 100 mL) and the combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 70 g/150 mL) with ethyl acetate (33–100% gradient) in heptane as the eluent and collection of pure fractions yielded 1.28 g (26%) of a colourless oil of low viscosity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, 3H), 1.28–1.41 (m, 2H), 1.44–1.55 (m, 2H), 2.62 (t, 2H), 3.88 (s, 2H), 7.29 (m, 1H), 7.38 (m, 1H), 7.51 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 20.6, 32.4, 47.0, 49.3, 112.8 (m), 121.1 (m), 123.5 (q), 130.5–131.6 (m), 130.8 (m), 132.0 (d), 160.8 (d).

(iv) Ethyl (2*S*)-3-[4-(2-{butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy) phenyl]-2-ethoxypropanoate

To a solution of *N*-butyl-*N*-[2-fluoro-4-(trifluoromethyl)benzyl]amine (0.598 g, 2.40 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.593 g, 2.00 mmol) in methylene chloride (20 mL) were added *N*,*N*-diisopropylethylamine (0.80 mL, 4.6 mmol) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (0.674 g, 2.10 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (100 mL) and the organic phase was washed with 2 M HCl (3 x 75 mL), saturated aqueous $NaHCO_3$ (2 x 75 mL), and brine (75 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 20 g/70 mL) with methanol (0–2% gradient) in methylene chloride as the eluent yielded 0.785 g (74%) of a pale yellowish-white oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–0.97 (m, 3H), 1.11–1.19 (m, 3H), 1.19–1.40 (m, 5H), 1.45–1.65 (m, 2H), 2.90–2.99 (m, 2H), 3.29–3.40 (m, 3H), 3.60 (m, 1H), 3.96 (m, 1H), 4.16 (q, 2H), 4.68 (s, 2H), 4.72 and 4.74 (2s, 2H, rotamers), 6.70 and 6.86 (2d, 2H, rotamers), 7.10 and 7.17 (2d, 2H, rotamers), 7.21–7.40 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 14.3, 15.2, 20.2, 29.2, 30.9, 38.5, 42.1 (d), 44.6 (d), 46.2, 47.5, 60.9, 66.3, 67.6, 68.3, 80.4, 113.0 (m), 114.3, 114.6, 121.4 (m), 123.3 (q), 128.5 (m), 129.1 (d), 130.6, 130.6, 130.7, 131.0 (d), 131.0–132.2 (m), 156.6, 156.8, 160.3 (d), 160.5 (d), 168.5, 168.6, 172.6. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

(v) (2*S*)-3-[4-(2-{Butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid

To a solution of ethyl (2*S*)-3-[4-(2-{butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoate (0.748 g, 1.42 mmol) in acetonitrile (70 mL) was added aqueous 0.10 M LiOH (35 mL) and the reaction mixture was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 0.688 g (97%) of a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–0.96 (m, 3H), 1.16 (t, 3H), 1.21–1.40 (m, 2H), 1.45–1.66 (m, 2H), 2.88–3.11 (m, 2H), 3.29–3.46 (m, 3H), 3.61 (m, 1H), 4.02 (m, 1H), 4.69 (s, 2H), 4.73 and 4.75 (2s, 2H, rotamers), 6.70 an 6.86 (2d, 2H, rotamers), 7.12 and 7.18 (2d, 2H, rotamers), 7.22–7.41 (m, 3H), 8.66 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 15.1, 20.1, 29.2, 30.8, 38.0, 42.2 (d), 44.6 (d), 46.3, 47.5, 66.8, 67.4, 68.1, 79.8, 113.0 (m), 114.4, 114.6, 121.4 (m), 123.3 (q), 128.3 (m), 129.1 (d), 130.2, 130.7, 130.8, 131.0 (d), 131.0–132.2 (m), 156.7, 156.9, 160.3 (d), 160.5 (d), 168.8, 168.9, 175.6. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

Example 2

(2*S*)-3-(4-{2-[(4-Chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(i) Ethyl (2*S*)-3-(4-{2-[(4-chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of *N*-(4-chlorobenzyl)-*N*-ethylamine (0.150 g, 0.88 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.270 g, 0.91 mmol) in methylene chloride (10 mL) were added *N*,*N*-diisopropylethylamine (0.34 mL, 1.9 mmol) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (0.320 g, 1.00 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (40 mL) and the organic phase was washed with 5% HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*.

Purification on a prepacked column of silica gel (Isolute® SPE Column, 50 g/150 mL) with methylene chloride/ethyl acetate 10:1 as the eluent yielded 0.24 g (61%) of a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05–1.24 (m, 9H), 2.88–3.00 (m, 2H), 3.28–3.42 (m, 3H), 3.60 (m, 1H), 3.96 (m, 1H), 4.12–4.20 (m, 2H), 4.56 and 4.58 (2s, 2H, rotamers), 4.64 and 4.73 (2s, 2H, rotamers), 6.75 and 6.88 (2d, 2H, rotamers), 7.09–7.20 (m, 4H), 7.24 and 7.30 (2d, 2H, rotamers).

(ii) (2*S*)-3-(4-{2-[(4-Chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2*S*)-3-(4-{2-[(4-chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (0.240 g, 0.54 mmol) in THF (30 mL) was added aqueous 0.10 M LiOH (15 mL) and the solution was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was acidified with 5% HCl and extracted with methylene chloride (2 x 50 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 2 g/15 mL) with ethyl acetate as the eluent afforded 0.138 g (61%) of a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05–1.21 (m, 6H), 2.94 (m, 1H), 3.04 (m, 1H), 3.30–3.45 (m, 3H), 3.61 (m, 1H), 4.01 (m, 1H), 4.57 and 4.58 (2s, 2H, rotamers), 4.66 and 4.73 (2s, 2H, rotamers), 6.74 and 6.87 (2d, 2H, rotamers), 7.10–7.20 (m, 4H), 7.24 and 7.30 (d, 2H), 7.98 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 13.9, 15.1, 38.0, 41.2, 41.5, 47.6, 49.8, 66.7, 67.4, 68.0, 79.8, 114.5, 114.6, 128.3, 128.8, 129.1, 129.5, 130.2, 130.7, 133.3, 133.6, 135.0, 135.7, 156.7, 156.9, 168.4, 168.4, 175.5. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

Example 3

(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]-propanoic acid

(i) *N*-[4-(Trifluoromethoxy)benzyl]acetamide

To a solution of 4-(trifluoromethoxy)benzylamine (3.46 g, 57.6 mmol) in DMF (75 mL) and acetic acid (10.0 g, 52.3 mmol) at –10 °C were added *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (20.2 g, 62.8 mmol) and *N*,*N*-diisopropylethylamine (20.0 mL, 115 mmol) and the reaction mixture was stirred at room temperature overnight. Ethyl

acetate (200 mL) was added and the organic phase was washed with water (100 mL), 0.25 M NaOH (100 mL), saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), 0.5 M HCl (100 mL), and water (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford 11.2 g (92%) of a colourless oil.

^1H NMR (600 MHz, $CDCl_3$): δ 2.03 (s, 3H), 4.43 (d, 2H), 5.83 (bs, 1H), 7.17 (d, 2H), 7.31 (d, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.9, 42.8, 120.5 (q), 121.1, 129.0, 137.3, 148.4, 170.6.

(ii) *N*-ethyl-*N*-[4-(Trifluoromethoxy)benzyl]amine

N-[4-(Trifluoromethoxy)benzyl]acetamide (10.4 g, 44.6 mmol) was dissolved in THF (100 mL) and cooled to −10 °C. Borane (56 mL of a 2 M solution of the dimethylsulfide complex in diethyl ether) was added and the reaction mixture was stirred at −10 °C for 15 minuters and was then allowed to warm to room temperature. The reaction mixture was refluxed overnight and was then allowed to cool to room temperature. The reaction was quenched by careful addition of 10% HCl (30 mL) at 0 °C and the mixture was stirred at room temperature overnight and then concentrated *in vacuo*. The residue was taken up in water (200 mL) and diethyl ether (200 mL) and the phases were separated. Concentration *in vacuo* of the diethyl ether phase afforded 1.9 g (21 %) of the title compound as a colourless oil.

^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, 3H), 2.72 (q, 2H), 3.83 (s, 2H), 3.86 (bs, 1H), 7.18 (d, 2H), 7.40 (d, 2H).

(iii) Ethyl (2*S*)-2-ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]propanoate

To a solution of *N*-ethyl-*N*-[4-(trifluoromethoxy)benzyl]amine (0.438 g, 2.00 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.593 g, 2.00 mmol) in methylene chloride (20 mL) were added *N,N*-diisopropylethylamine (0.80 mL, 4.6 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.674 g, 2.10 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (40 mL) and the organic phase was washed with 5% HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 50 g/150 mL) with methylene chloride/ethyl acetate 10:1 as the eluent yielded 0.57 g (58%) of a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08–1.28 (m, 9H), 2.88–3.00 (m, 2H), 3.28–3.44 (m, 3H), 3.60 (m, 1H), 3.96 (m, 1H), 4.12–4.20 (m, 2H), 4.60 and 4.62 (2s, 2H, rotamers), 4.66 and 4.74 (2s, 2H, rotamers), 6.74 and 6.89 (2d, 2H, rotamers), 7.08–7.27 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 14.0, 14.4, 15.2, 38.6, 41.1, 41.5, 47.5, 49.7, 61.0, 66.3, 67.7, 68.3, 80.4, 114.5, 114.6, 121.2, 121.5, 128.3, 129.5, 130.6, 130.7, 130.7, 135.6, 136.1, 148.6, 156.9, 168.1, 168.2, 172.6. (The number of peaks is larger than the number of carbons due to rotamers. Trifluorinated carbon not reported.)

(iv) (2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]-propanoic acid

To a solution of ethyl (2*S*)-2-ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]propanoate (0.560 g, 1.13 mmol) in THF (50 mL) was added aqueous 0.10 M LiOH (25 mL) and the solution was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 10 g/70 mL) with ethyl acetate as the eluent afforded 0.457 g (87%) of a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08–1.23 (m, 6H), 2.96 (m, 1H), 3.08 (m, 1H), 3.33–3.43 (m, 2H), 3.48 (m, 1H), 3.59 (m, 1H), 4.05 (m, 1H), 4.60 and 4.62 (2s, 2H, rotamers), 4.67 and 4.75 (2s, 2H, rotamers), 6.75 and 6.89 (2d, 2H, rotamers), 7.09–7.27 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 14.0, 15.2, 37.8, 41.2, 41.6, 47.5, 49.7, 67.0, 67.6, 68.2, 79.8, 114.6, 114.8, 121.2, 121.5, 128.3, 129.5, 129.9, 130.8, 130.8, 135.4, 136.0, 148.7, 148.8, 156.9, 157.0, 168.3, 168.3, 174.2. (The number of peaks is larger than the number of carbons due to rotamers. Trifluorinated carbon not reported.)

Example 4

(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl] propanoic acid

(i) Ethyl (2*S*)-2-ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy) phenyl] propanoate

To a solution of *N*-ethyl-*N*-[4-(trifluoromethyl)benzyl]amine (0.213 g, 1.05 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.296 g, 1.00 mmol) in methylene chloride (10

mL) were added *N,N*-diisopropylethylamine (0.40 mL, 2.3 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.337 g, 1.05 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (90 mL) and the organic phase was washed with 5% HCl (2 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 50 g/150 mL) with methanol (0–1% gradient) in methylene chloride as the eluent yielded 0.339 g (70%) of a colourless oil.

^1H NMR (400 MHz, $CDCl_3$): δ 1.06–1.24 (m, 9H), 2.88–3.00 (m, 2H), 3.28–3.44 (m, 3H), 3.59 (m, 1H), 3.96 (m, 1H), 4.10–4.19 (m, 2H), 4.64, 4.67, and 4.74 (3s, 4H, rotamers), 6.71 and 6.88 (2d, 2H, rotamers), 7.10 and 7.17 (2d, 2H, rotamers), 7.30 (d, 2H), 7.52 and 7.57 (2d, 2H, rotamers).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 13.9, 14.3, 15.1, 38.5, 41.2, 41.7, 47.8, 49.9, 60.8, 66.2, 67.6, 68.2, 80.3, 114.4, 114.5, 125.5 (m), 125.8 (m), 127.1, 128.2, 129.2–130.6 (m), 130.5, 130.6, 130.6, 141.0, 141.5, 156.6, 156.8, 168.1, 168.2, 172.5. (The number of peaks is larger than the number of carbon atoms due to rotamers. Trifluorinated carbon not reported.)

(ii) (2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl] propanoic acid

To a solution of ethyl (2*S*)-2-ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl] propanoate ((0.308 g, 0.64 mmol) in acetonitrile (32 mL) was added aqueous 0.10 M LiOH (16 mL) and the solution was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was diluted with water and aqueous 0.10 M LiOH (to a total volume of 100 mL, pH~10) and washed with diethyl ether (2 x 100 mL). The aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with 5% HCl (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 0.279 g (96%) of a colourless oil.

^1H NMR (400 MHz, $CDCl_3$): δ 1.08–1.24 (m, 6H), 2.88–3.12 (m, 2H), 3.34–3.47 (m, 3H), 3.61 (m, 1H), 4.02 (m, 1H), 4.66, 4.67, 4.69, and 4.76 (4s, 4H, rotamers), 6.72 and 6.89 (2d, 2H, rotamers), 7.12 and 7.19 (2d, 2H, rotamers), 7.32 (d, 2H), 7.53 and 7.58 (2d, 2H, rotamers), 8.08 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 13.9, 15.1, 38.0, 41.4, 41.9, 48.0, 50.1, 66.8, 67.5, 68.1, 79.8, 114.5, 114.7, 125.6 (m), 125.9 (m), 127.2, 128.2, 129.2–130.6 (m), 130.2, 130.7, 130.8, 140.8, 141.3, 156.7, 156.9, 168.6, 168.6, 175.5. (The number of peaks is larger than the number of carbon atoms due to rotamers. Trifluorinated carbon not reported.)

Example 5

(2*S*)-3-[4-(2-{Butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid

(i) Ethyl (2*S*)-3-[4-(2-{butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoate

To a solution of *N*-butyl-*N*-[4-(trifluoromethyl)benzyl]amine (0.486 g, 2.10 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.593 g, 2.00 mmol) in methylene chloride (20 mL) were added *N*,*N*-diisopropylethylamine (0.80 mL, 4.6 mmol) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (0.674 g, 2.10 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (80 mL) and the organic phase was washed with 5% HCl (3 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 70 g/150 mL) with methanol (0–1% gradient) in methylene chloride as the eluent and collection of pure fractions yielded 0.355 g (35%) of a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82–0.93 (m, 3H), 1.09–1.17 (m, 3H), 1.20 (t, 3H), 1.22–1.38 (m, 2H), 1.44–1.61 (m, 2H), 2.87–3.00 (m, 2H), 3.25–3.39 (m, 3H), 3.59 (m, 1H), 3.96 (m, 1H), 4.08–4.18 (m, 2H), 4.64, 4.68, and 4.75 (3s, 4H, rotamers), 6.72 and 6.87 (2d, 2H, rotamers), 7.10 and 7.17 (2d, 2H, rotamers), 7.29 (d, 2H), 7.51 and 7.56 (2d, 2H, rotamers).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 14.0, 14.9, 19.9, 29.0, 30.5, 38.3, 45.9, 46.7, 48.1, 50.1, 60.6, 66.0, 67.3, 67.9, 80.1, 114.2, 114.3, 125.3 (m), 125.6 (m), 126.9, 127.9, 128.8–130.5 (m), 130.2, 130.3, 130.4, 141.0, 141.4, 156.5, 156.7, 168.1, 172.2. (The number of peaks is larger than the number of carbon atoms due to rotamers. Trifluorinated carbon not reported.)

(ii) (2*S*)-3-[4-(2-{Butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxy propanoic acid

To a solution of ethyl (2*S*)-3-[4-(2-{butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy) phenyl]-2-ethoxypropanoate (0.311 g, 0.61 mmol) in acetonitrile (30 mL) was added aqueous

0.10 M LiOH (15 mL) and the solution was stirred at room temperature overnight. After acidification with 5% HCl, the mixture was extracted with ethyl acetate (3 x 100 mL) and the combined organic phase was washed with 5% HCl (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 0.232 g (79%) of a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–0.94 (m, 3H), 1.10–1.19 (m, 3H), 1.20–1.36 (m, 2H), 1.46–1.62 (m, 2H), 2.87–3.10 (m, 2H), 3.25–3.45 (m, 2H), 3.61 (m, 1H), 4.01 (m, 1H), 4.66, 4.69 and 4.76 (3s, 4H, rotamers), 6.72 and 6.88 (2d, 2H, rotamers), 7.12 and 7.19 (2d, 2H, rotamers), 7.30 (d, 2h), 7.53 and 7.59 (2d, 2H, rotamers), 8.27 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 15.1, 20.1, 29.2, 30.7, 38.0, 46.3, 47.0, 48.4, 50.4, 66.7, 67.4, 68.1, 79.8, 114.5, 114.6, 125.6 (m), 125.9 (m), 127.1, 128.2, 129.2–130.5 (m), 130.2, 130.7, 130.8, 140.8, 141.2, 156.7, 156.9, 168.8, 175.6. (The number of peaks is larger than the number of carbon atoms due to rotamers. Trifluorinated carbon not reported.)

BIOLOGICAL ACTIVITY

The compounds of the invention were tested in the assays described in WO03/051821.

The compounds of formula I have an EC_{50} of less than 0.1μmol/l for PPARα and particular compounds have an EC_{50} of less than 0.01μmol/l. Additionally in particular compounds the ratio of the EC_{50} (PPARγ) : EC_{50} (PPARα) is greater than 150:1. It is believed that this ratio is important with respect to the pharmacological activity of the compounds and to their therapeutic profile.

In addition the compounds of the present invention exhibit improved DMPK (Drug Metabolism and Pharmacokinetic) properties for example they exhibit improved metabolic stability *in vitro*. The compounds also have a promising toxicological profile.

The EC_{50}s of the Examples for human PPAR alpha are:

Example 1 0.001μmol/l;

Example 2 0.003μmol/l;

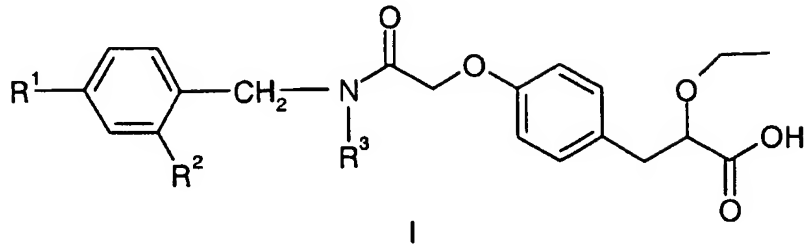
Example 3 0.003μmol/l;

Example 4 0.005μmol/l; and

Example 5 0.003μmol/l

Claims:

1. The S enantiomer of a compound of formula I



I

wherein R^1 represents chloro, trifluoromethyl or trifluoromethoxy, R^2 represents H or fluoro and R^3 represents a C_{2-4}alkyl group as well as pharmaceutically acceptable salts, solvates and prodrugs thereof.

2. A compound selected from:
(2*S*)-3-[4-(2-{Butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxy propanoic acid;
(2*S*)-3-(4-{2-[(4-Chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid;
(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]-propanoic acid;
(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl] propanoic acid; and
(2*S*)-3-[4-(2-{Butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid;
and pharmaceutically acceptable salts and solvates thereof.

3. (2*S*)-3-[4-(2-{Butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxy propanoic acid and pharmaceutically acceptable salts thereof.

4. 2*S*)-3-(4-{2-[(4-Chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid and pharmaceutically acceptable salts thereof.

5. (2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]-propanoic acid and pharmaceutically acceptable salts thereof.

6. (2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl] propanoic acid and pharmaceutically acceptable salts thereof.

7. 2*S*)-3-[4-(2-{Butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid and pharmaceutically acceptable salts thereof.

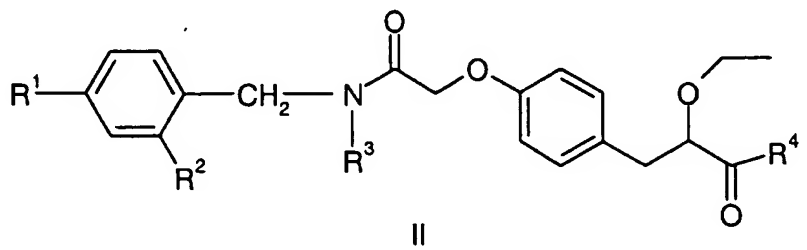
8. A pharmaceutical formulation comprising a compound according to any one of claims 1 to 7 in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

9. A method of treating or preventing lipid disorders (dyslipidemia) whether or not associated with insulin resistance comprising the administration of a compound according to any one of claims 1 to 7 to a mammal in need thereof.

10. The use of a compound according to any one of claims 1 to 7 in the manufacture of a medicament for the treatment of lipid disorders (dyslipidemia) whether or not associated with insulin resistance.

11. A method of treating or preventing type 2 diabetes comprising the administration of an effective amount of a compound of formula I according to any one of claims 1 to 7 to a mammal in need thereof.

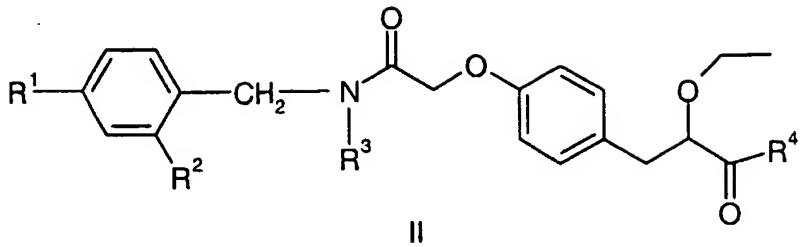
12. A process for the preparation of a compound of formula I comprising reacting the S-enantiomer of a compound of formula II



II

in which R^1, R^2 and R^3 are as previously defined and R^4 represents a protecting group for a carboxylic hydroxy group with a de-protecting agent.

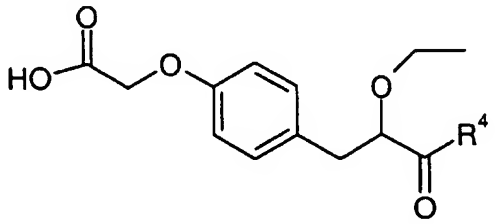
13. A compound of formula II



II

in which R^1, R^2 and R^3 are as previously defined and R^4 represents a protecting group for a carboxylic hydroxy group.

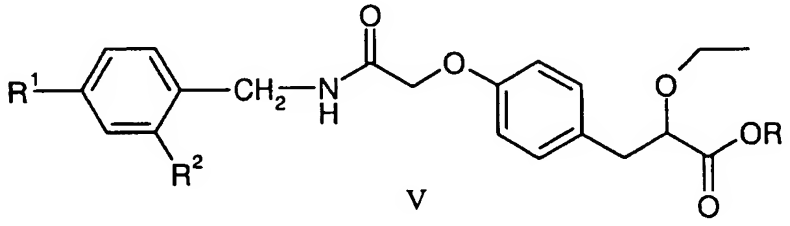
14. A compound of formula III



III

in which R^4 represents a protecting group for a carboxylic hydroxy group.

15. A process for the preparation of a compound of formula I comprising reacting a compound of formula V,



V

in which R^1 and R^2 are as previously defined, and R is H or OR represents a protecting group for a carboxylic hydroxy group with a compound of formula VI

R^3X

VI

wherein R^3 is as previously defined and X is a leaving group, in the presence of a base in the presence of an inert solvent at a temperature in the range -25°C to 150°C and optionally, when OR represents a protecting group, removal of the protecting group.

16. A compound of formula V selected from
(2*S*)-3-[4-(2-{[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxy propanoic acid;
(2*S*)-3-(4-{2-[4-Chlorobenzylamino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid;
(2*S*)-2-Ethoxy-3-[4-(2-{4-(trifluoromethoxy)benzylamino}-2-oxoethoxy)phenyl]propanoic acid; and
(2*S*)-2-Ethoxy-3-[4-(2-{4-(trifluoromethyl)benzylamino}-2-oxoethoxy)phenyl] propanoic acid.

17. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 7 combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity.

18. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 7 combined with another PPAR modulating agent.

19. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 7 combined with a cholesterol-lowering agent.

20. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 7 combined with a HMG-CoA reductase inhibitor.

21. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 7 combined with atorvastatin or a pharmaceutically acceptable salt, solvate, crystalline form or prodrug thereof.

22. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 7 combined with rosuvastatin or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 7 combined with an IBAT inhibitor.

24. A pharmaceutical composition according to claim 23 wherein the IBAT inhibitor is selected from one of:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl) carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(5-carboxypentyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{(R)-1-[*N''*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]-2-hydroxyethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-((ethoxy)(methyl)phosphoryl-methyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(hydroxy)(methyl)phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-methylthio-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(ethyl) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(hydroxy) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[(R)-*N'*-(2-methylsulphinyl-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-[*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-{(S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R/S)-α-{*N*-[1-(R)-2-(S)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl}-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/05602

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C235/20 A61K31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2003 051822 A (ASTRAZENECA AB, SWED.;ASTRAZENECA UK LIMITED) 26 June 2003 (2003-06-26) the whole document	1-24
P,X	WO 2003 051821 A (ASTRAZENECA AB, SWED.;ASTRAZENECA UK LIMITED) 26 June 2003 (2003-06-26) the whole document	1-24
A	US 6 258 850 B1 (ANDERSSON KJELL) 10 July 2001 (2001-07-10) cited in the application the whole document	1-24

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 April 2004	26/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lorenzo Varela, M.J.

INTERNATIONAL SEARCH REPORT

.....rnational application No.
PCT/GB 03/05602

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9 and 11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound, Rule 39.1 (iV) PCT.

2. [X] Claims Nos.: 1,8-15,17-24 all partially
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,8-15,17-24 all partially

Present claims 1, 8-15 and 17-24 relate to an extremely large number of possible compounds or pharmaceutical compositions due to the term "prodrug" or hte expression "protecting group for carboxylic hydroxy group" comprised in those claims. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/compositions/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula (I) and compounds of formulae (II), (III) and (V) wherein the protecting group is an ester according to the description and the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/GB 03/05602

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2003051822 A	26-06-2003	WO 03051821 A1	26-06-2003
		WO 03051822 A1	26-06-2003
WO 2003051821 A	26-06-2003	WO 03051821 A1	26-06-2003
		WO 03051822 A1	26-06-2003
US 6258850 B1	10-07-2001	AT 246674 T	15-08-2003
		AT 251130 T	15-10-2003
		AU 752261 B2	12-09-2002
		AU 4667199 A	20-12-1999
		AU 752262 B2	12-09-2002
		AU 4667299 A	20-12-1999
		BR 9910921 A	06-03-2001
		BR 9910928 A	13-02-2001
		CA 2333938 A1	09-12-1999
		CA 2334374 A1	09-12-1999
		CN 1311772 T	05-09-2001
		CN 1312795 T	12-09-2001
		DE 69910203 D1	11-09-2003
		DE 69911770 D1	06-11-2003
		DK 1084103 T3	17-11-2003
		DK 1084102 T3	02-02-2004
		EE 200000720 A	15-04-2002
		EE 200000725 A	17-06-2002
		EP 1084103 A1	21-03-2001
		EP 1084102 A1	21-03-2001
		HK 1035711 A1	02-01-2004
		HR 20000782 A1	30-06-2001
		HU 0103226 A2	28-01-2002
		HU 0103376 A2	29-05-2002
		ID 28833 A	05-07-2001
		ID 29457 A	30-08-2001
		JP 2002516899 T	11-06-2002
		JP 2002516900 T	11-06-2002
		JP 2004043480 A	12-02-2004
		NO 20006115 A	07-02-2001
		NO 20006116 A	02-02-2001
		NZ 508452 A	30-05-2003
		NZ 508453 A	30-06-2003
		PL 344681 A1	19-11-2001
		PL 345205 A1	03-12-2001
		PT 1084103 T	31-12-2003
		RU 2214999 C2	27-10-2003
		WO 9962872 A1	09-12-1999
		WO 9962871 A1	09-12-1999
		SI 1084103 T1	31-12-2003
		SI 1084102 T1	29-02-2004
		SK 17682000 A3	06-08-2001
		SK 17692000 A3	10-05-2001
		TR 200003581 T2	21-06-2001
		TR 200003583 T2	21-05-2001
		TW 446696 B	21-07-2001
		TW 548263 B	21-08-2003